NTP
National Toxicology Program

Draft NTP Monograph on Health Effects of Low-level Lead:
Kidney Effects

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Peer Review Meeting
November 17-18, 2011

Kidney Effects

- Principal health effect of Pb
  - Reduced glomerular filtration rate (GFR)
- EPA (2006) and ATSDR (2007) conclude Pb
  - Can cause clinically relevant kidney effects
    - At levels of exposure in the general population when other risk factors present (EPA)
    - Threshold cannot be determined (EPA)

Glomerular Filtration Rate (GFR)

- **Outcomes considered**
  - Serum creatinine
  - Creatinine clearance
  - estimated GFR (eGFR)
  - Chronic kidney disease (CKD)

NTP conclusion:

sufficient evidence in adults and *limited* evidence in adolescents that blood Pb levels <10µg/dL (and <5µg/dL) are associated with decreased kidney function

inadequate evidence that blood Pb levels <10µg/dL are associated with kidney effects in children less than 12 years of age

Kidney Effects in Adults & Adolescents

- Consistency in findings from ~15 publications (Table 7.3)
  - Mostly cross-sectional studies, several prospective
  - Not necessarily for every main finding within a study, but for overall study interpretation
    - Sub-analyses based on disease state, gender, exposure measure
- Associations below mean blood Pb <5µg/dL (Akesson 2005, Muntner 2005, Navas-Acien 2009, Yu 2004, Fadrowski 2010*)
- Associations stronger in certain patient populations
  - Diabetics (Normative Aging Study, Tsaih 2004) and hypertensives (NHANES, Muntner 2003)
  - Prospective studies of CKD or diabetic patients from Taiwan (Yu 2004, Lin 2003, 2006a, 2006b)
- Supported by animal data

*NHANES (1988-1994) 769 ♂♀, 12-20y

Reverse Causality

- Impaired kidney function → less efficient Pb elimination → higher internal Pb exposure estimates
- Not sufficient to account for associations
  - CKD patient studies: Baseline blood and EDTA-chelatable Pb predict kidney function decline over 4 years (Yu 2004)
  - Associations observed in the normal range of kidney function (Kim 1996, Tsaih 2004)
  - Renal failure does not increase bone lead stores, blood lead, or chelatable lead in subjects with and without renal failure (Van de Vyver 1988, Batuman 1983, Emmerson 1973)

Kidney Effects in Children <12 Years

NTP Conclusions: *inadequate* evidence that blood Pb levels <10µg/dL are associated with kidney effects in children less than 12 years of age:

- Measures of GFR used in adult studies often not available
  - Some include serum creatinine
- Studies report "early biological effect markers"
  - e.g., β_2-microglobulin, NAG, retinol binding protein
  - Less clear interpretation as prognostic variables
  - Findings inconsistent

The NTP's Conclusions for Kidney Effects

There is *sufficient* evidence in adults and *limited* evidence in adolescents that blood Pb levels <5µg/dL are associated with adverse effects on kidney function and there is *inadequate* evidence to evaluate kidney effects in children.

Specific Kidney Charge Questions

i. Please comment on whether the scientific evidence presented supports the NTP's conclusions.

ii. Please comment on whether you agree/disagree with the NTP's conclusions. Explain why. Identify any references that should be cited.

Table 7.5: NTP conclusions on kidney effects of low level Pb

Health Effect	Population	Conclusion	Blood Pb Evidence	Bone Pb Evidence
Increased Chronic Kidney Disease (CKD) and decreased Glomerular Filtration Rate (GFR)	Adults	*Sufficient*	Yes, <5µg/dL	Not studied
	Children age 12 or older	*Limited*	Yes, <5µg/dL	Not studied
	Children under 12	*Inadequate*	Unclear	Not studied

d. Other Kidney Effects

i. Please comment on whether there are additional kidney effects in humans that may be adversely affected by low-level Pb exposure that you would recommend adding to the document.

Please comment on whether and how the additional kidney effects would affect the overall conclusions for health effects associated with blood Pb levels <10µg/dL.

A. General Questions

1) Is the text in the draft monograph articulated clearly and correctly? Are the summary sections useful? Are the tabular information and format easily understandable? If not, please identify the specific sections that need improvement and provide specific suggestions for improvement.

2) Is the information in the draft monograph's text and tables presented objectively?
If not, please identify the specific sections that need improvement and provide specific suggestions for improvement.

CKD, Creatinine Clearance & eGFR

	Reference	Population	Design	Main Finding	Blood Pb (µgdL)
CKD	Muntner 2003	US (NHANES 1988-1994) 10,398 ♂♀, no hypertension	CS	1.09(95%CI: 0.41,2.89) adjOR	4.7-52.9 vs 0.7-1.6
	Muntner 2003	US (NHANES 1988-1994) 4,813 ♂♀, hypertension	CS	1.85(95%CI: 1.32,2.59) adjOR*	3.9-5.9 vs 0.7-2.4
	Muntner 2005	US (NHANES 1999-2002) 9,961 ♂♀	CS	1.89(95%CI: 1.09,3.3) adjOR*	1.63-2.47 vs <1.06
creatinine clearance	Akesson 2005	Sweden (Lund, WHILA) 816 ♀	CS	-0.18(95%CI: -0.3,-0.06) adjβ*	2.2 (5-95th 1.1-4.6)
	Payton 1994	US (Boston, Norm. Aging) 744 ♂	CS	=-0.0403(SE: 0.0198) adjβ*, ln Pb	8.1 (<5-26)
	Staessen 1992	Belgium (multi-site, Cadmibel) 1,981 ♂♀	CS	3.76(95%CI: 1.37,10.4) adjOR* for impaired clearance per 10-fold ↑ Pb	♂11.4 (2.3-72.5) ♀7.5 (1.7-60.3)
	Wu 2003*	US (Boston, Norm. Aging) 709 ♂	CS	no assoc. w/est. creatinine clearance (associated with patella Pb)	6.2 (0-35)
eGFR (mL/min/1.73 m²)	Akesson 2005	Sweden (Lund, WHILA) 816 ♀	CS	-0.2(95%CI: -0.32,-0.09) adjβ*	2.2 (5-95th 1.1-4.6)
	Fadrowski 2010	US (NHANES 1988-1994) 769 ♂♀, 12-20y	CS	-6.6 (95%CI: -0.7,-12.6), mean difference*	>2.9 vs <1
	Navas-Acien 2009	US (NHANES 1999-2006) 14,778 ♂♀	CS	1.56(95%CI: 1.17,2.08) adjOR* ↓ eGFR	>2.4 vs <1.1
	Yu 2004	Taiwan (CKD patients) 121 ♂♀	Pros	-4.2 over 4y per 1 µg/dL increase baseline Pb*	4.2 (1-13.4)

not-supportive supportive

Serum Creatinine

Reference	Population	Design	Main Finding	Blood Pb (µgdL)	Age	BMI	Sex	Blood Pressure	Diabetes	Alcohol	Smoking	Medication
Kim 1996	US (Boston, Norm. Aging 1979-1994) 141 ♂	cohort	0.039(SE: 0.025) adjβ blood Pb≤10 µg/dL and SCΔ (acceleration of age-related increases at higher exposures)	9.9 (0.2-54.1)	X	X	X	X	.	X	X	.
Tsaih 2004	US (Boston, Norm. Aging ♂, non-diabetics)	cohort	0.006(SE: 0.005) adjβ w/baseline Pb and SCΔ	6.5 at baseline	X	X	.	X	X	X	X	X
Kim 1996	US (Boston, Norm. Aging 1979-1994) 141 ♂	cohort	0.06(SE: 0.019) adjβ blood Pb≤10 and SC*	9.9 (0.2-54.1)	X	X	X	X	.	X	X	.
Tsaih 2004	US (Boston, Norm. Aging ♂, diabetics)	cohort	0.076(SE: 0.023) adjβ w/baseline Pb and SCΔ*	6.5 at baseline	X	X	.	X	X	X	X	X
de Burbure 2003	France (multi-site) 244 ♀	CS	[1.101(95%CI: 0.678,1.787) crudeOR]	5.3 (exp) v 4.2 (ref)	X	.	X	.	.	.	.	.
de Burbure 2003	France (multi-site) 235 ♂	CS	[1.075(95%CI: 0.666,1.735) crudeOR]	6.8 (exp) v 7.1 (ref)	X	.	X	.	.	.	.	.
Muntner 2003	US (NHANES 1988-1994) 10,398 ♂♀, no hypertension	CS	1.09(95%CI: 0.53,2.22) adjOR	4.7-52.9 vs 0.7-1.6	X	X	X	X	X	X	X	.
Pocock 1984	England (multi-site, Regional Heart Study) 7,364 ♂	CS	0=β, NS	<12.4 - 37.3	X	.	X	.	.		.	.
Staessen 1990	England (civil servants) 133 ♀	CS	no assoc. w/serum creatinine (r = 0.03)	10.2	X	.	X	.	.	.	.	.
Wu 2003*	US (Boston, Norm. Aging ♂)	CS	no assoc. w/serum creatinine (associated with patella Pb)	6.2 (0-35)	X	X	.	X	.	X	X	X
Lai 2008	Taiwan (rural, aborginal & non-aboriginl) 2,365 ♂♀	CS	1.92(95%CI: 1.18,3.1) adjOR*	5.3-5.6 (range of averages)	X	.	X	X	.	X	X	.
Muntner 2003	US (NHANES 1988-1994) 4,813 ♂♀, hypertension	CS	1.47(95%CI: 1.03,2.1) adjOR*	3.9-5.9 vs 0.7-2.4	X	X	X	X	X	X	X	.
Staessen 1990	England (civil servants) 398 ♂	CS	(+) assoc. w/serum creatinine (r = 0.10)*	12.4	X	.	X	.	.	.	.	.

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Excerpt from Table 7.4: Kidney Outcomes in Cross-Sectional Studies in Children Less than 12 Years of Age			
Conclusion	**Study Description**	**Key Findings**	**Reference**
Supporting	Children aged 17 years living near chemical-industry areas in Belgium; n=100 Pb and 100 referent	↑ Levels of serum β2 microglobulin in children with higher blood Pb (mean= 2.7µg/dL) compared to referents (mean= 1.5µg/dL)	Staessen (2001)
Supporting	Children aged 1-6 years of workers in Pakistani lead smelters and battery recycling plants; n=123 Pb and 123 referent	↑ levels of serum creatinine and urea in Pb-exposed children compared to controls (median Pb = 8.1 and 6.7 µg/dL; respectively; $p \leq 0.01$ for both measures in unadjusted analyses)	Khan (2010)
Equivocal	Children aged 12-15 years in Czech Republic living near two smelters; n=91 area #1, 53 area #2, and 51 in referent site	↑Levels of levels of urinary β_2-microglobulin in children living in area #1 (blood Pb: male= 10.9 µg/dL; female = 9.44 µg/dL) compared to referents (blood Pb: male= 8.7 µg/dL; female = 8.39 µg/dL), but not area #2 where blood Pb levels were highest (blood Pb: male= 14.9 µg/dL; female = 12.9 µg/dL)	Bernard (1995)
Equivocal	Children aged 10 years in Poland living near Pb-producing factories; n=62 and 50 referent	Altered urinary β2 microglobulin between 62 exposed (blood Pb = 13.3 µg/dL) and 50 control (blood Pb = 3.9 µg/dL) children; no difference in serum creatinine	Fels (1998)
Not supporting	Children aged 8.5-12.3 years in France living near two smelters; n=200 and 200 age/gender matched referents	No difference in urinary β2-microblobulin in children living in reference (mean blood Pb: male = 3.4 µg/dL; female= 2.7 µg/dL) and polluted areas (mean blood Pb: male = 4.2 µg/dL; female = 3.7 µg/dL)	de Burbure (2003)
Not supporting because of direction of effect	Children aged 8.5-12.3 years in Europe living near two smelters; n=364 and 352 age/gender matched referents	Negative relationship (regression coefficients) with blood lead and serum creatinine (-0.026, p=0.007) and β_2-microglobulin (-0.095, p=0.01) in children living near smelters (mean Pb: male=4.2; female 3.6 µg/dL) compared to controls (mean Pb: male=3.4; female=2.8 µg/dL)	de Burbure (2006)

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